RHEUMATIC MITRAL STENOSIS WITH LEFT ATRIAL APPENDAGE THROMBUS–EFFECT OF ORAL ANTICOAGULATION ON LEFT ATRIAL APPENDAGE THROMBUS RESOLUTION

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Certificate

This is to certify that **Dr C.Elangovan**, Post graduate student [2003-2006] in the Department of Cardiology, Government General Hospital Chennai & Madras Medical College, Chennai -03, has done this Dissertation on **"RHEUMATIC MITRAL STENOSIS WITH LEFT ATRIAL APPENDAGE THROMBUS – EFFECT OF ORAL ANTICOAGULATION ON LEFT ATRIAL APPENDAGE THROMBUS RESOLUTION"** under my guidance and supervision in partial fulfillment of the regulations laid down by The Tamil Nadu Dr M.G.R Medical University, Chennai, for DM Cardiology –Branch II examination to be held in February 2006.

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RHEUMATIC MITRAL STENOSIS WITH LEFT ATRIAL APPENDAGE THROMBUS – EFFECT OF ORAL ANTICOAGULATION ON LEFT ATRIAL APPENDAGE THROMBUS RESOLUTION

LIST OF ABBREVIATIONS

AF- Atrial fibrillation

AF-I- Intermittent atrial fibrillation

ACC –American College of cardiology

AHA- American Heart Association

TTE-Transthoracic echocardiography

TEE-Transesophageal echocardiography

MS-Mitral stenosis

MR-Mitral regurgitation

TR-Tricuspid regurgitation

AR –Aortic regurgitation

TS-Tricuspid stenosis

MV -Mitral valve

LA-Left atrium

LV-Left ventricle

LAA-Left atrial appendage

PG-Peak gradient; **MG-**mean gradient

PLAX- Parasternal long axis

PSAX-Parasternal short axis

A4C- Apical four chamber view

SEC-Spontaneous echo contrast

LASEC Left atrial Spontaneous echo contrast

PHT-Pulmonary hypertension

EF-Ejection fraction

INR- International normalized ratio

SD-Standard deviation

NYHA- New York Heart Association

CMC-Closed mitral commissurotomy

BMV- Balloon mitral Valvotomy

PTMC-Percutaneous Transluminal mitral commissurotomy

CONTENTS

INTRODUCTION

Rheumatic heart disease is one of the commonest cardiac condition in India in both children and adults, accounting for 30- 40 % of cardiac cases admitted in hospital. Approximately 25% of all patients with rheumatic heart disease have pure or predominant mitral stenosis (MS). Thromboembolism develops in at least 20% of mitral stenosis patients, at some point of time during the course of their disease. Thromboembolism remains an important cause of morbidity and mortality in rheumatic MS.

Cardiogenic embolism in mitral stenosis is most often due to left atrial (LA) thrombi and at times due to mitral valve vegetation. Left atrial appendage (LAA) is the commonest site from where the thrombus originates.

Echocardiography is the widely used method for detecting left atrial and left atrial appendage thrombi. Transthoracic echocardiography (TTE) is only 50% sensitive in detecting LA and LAA thrombi. Transesophageal echocardiography (TEE) is superior to TTE and is 99% sensitive and specific in detecting LA and LAA thrombi.

Left atrial spontaneous echo contrast (LASEC) or “Smoke” occurs in conditions that favours stasis of blood .It is associated with an increased risk of LA thrombus formation and arterial embolization and is better identified by TEE.

Medical treatment for LA and LAA thrombus in rheumatic MS is still unclear. Several studies indicate that adequate anticoagulation using oral anticoagulants in those with atrial fibrillation and in those with documented thrombus reduce the frequency of thromboembolic phenomena.

However there are not enough data whether anticoagulation resolves or reduces size of LA thrombus in patients with rheumatic MS, and thus simplifying hence simplifying surgical or interventional treatment for diseased valves otherwise suitable for closed mitral comissurotomy (CMC) or balloon mitral valvotomy (BMV).

AIM OF THE STUDY

Left atrial (LA) thrombus formation remains a significant problem causing morbidity and mortality in rheumatic mitral stenosis.

Medical treatment for this condition still remains unclear. This study is aimed

1. To study the effect of oral anticoagulation on resolution of left atrial appendage thrombus.
2. To analyse various factors associated with resolution or reduction in size of left atrial appendage thrombus.
3. To analyse effect of oral anticoagulation on left atrial spontaneous echo contrast.

BACKGROUND

Rheumatic heart disease remains one of the commonest acquired heart diseases affecting young and middle aged population in our country.

Pure or predominant Mitral stenosis (MS) is the commonest presenting manifestation of chronic rheumatic heart disease accounting for 25% percentage of all cases. Females outnumber males by two fold, affected by rheumatic MS.

Left atrial thrombus formation is an important complication of rheumatic MS causing morbidity and mortality.

In one study 17% of patients undergoing surgery for mitral stenosis have left atrial thrombus and in about two third of these patients, the thrombus is restricted to left atrial appendage (LAA).

Deverall et al.[1] reported that 16% of patients evaluated for MS had a history of systemic embolism.

In approximately 10-15% of patients with MS systemic embolic manifestation due to left atrial thrombus may be the first symptom. Cerebral embolism constitutes 60-70 % of episodes of systemic embolism in several series.

Emboli are often fatal in patients with mitral stenosis. In a 10 year follow-up of 250 patients with unoperated MS, Rowe et al[2], found that 19% of 110 deaths in the first 10 years of follow-up are due to systemic embolism. In the follow-up series of Olesen[3], 22% of all deaths in MS were due to thromboembolism.

Several studies reported that the following factors are associated with left atrial thrombus formation in MS.

1. Atrial fibrillation
2. Age-Higher the age, greater the risk.
3. Left atrial size.

4. Left atrial spontaneous echo contrast.

5. LV systolic dysfunction

The severity of mitral stenosis does not correlate with risk of thrombus formation.

On the other hand presence of significant mitral regurgitation is a negative predictor of development of left atrial thrombus .This may be due to an increase in flow velocity with in left atrium in systole created by MR.

In the classical series of Coulshed et al[4], 737 patients with predominant mitral stenosis were followed up for cardiac events. Of 248 patients .0f 35 years or less, the incidence of embolisation was 9% .Of 489 patients over 35 years ,the incidence was 24%. Deveral et al[1], found that incidence of systemic emboli correlates better with years since initial rheumatic activity than chronological age per se.

ATRIAL FIBRILLATION (AF)

Atrial fibrillation is another important factor associated with left atrial thrombus .Most of the MS patients who have systemic embolism are in AF. The prevalence of AF increases with age.

Eighty percent of patients with MS, in whom systemic emboli develop, are in atrial fibrillation (AF). The combination of MS and AF increases the chances of stroke 17 fold.

There is seven time greater risk of stroke in patients with MS in AF, when compared with those with MS in sinus rhythm (SR). Just the presence of MS and AF, is said to confer the greatest risk for thromboembolism.

In coulshed et al[4] .series, in those over 35 years of age, the incidence of systemic embolism was 32 % in those with AF as against 11% in those in sinus rhythm.

When atrial fibrillation supervenes, blood flow in the atrial appendage and in the body of the left atrium becomes more disorganised, with low velocity, multidirectional flow patterns, blood flow stasis, and development of atrial thrombi.

This swirling pattern of low velocity flow often is evident as spontaneous echo contrast in echocardiography, particularly when using a high frequency transducer from transesophageal approach.

LEFT ATRIAL SIZE

Left atrial size is assessed by various methods .Most commonly left atrial dimension measured by M-mode in transthoracic parasternal long axis (PLAX) at the level of aortic valve level. The measurement is made at end-systole, just before mitral valve opening when the left atrial volume is maximal. In addition various studies indicated that left atrial volume is a powerful prognostic factor in variety of situations

Left atrial dimensions were measured in end systole in PLAX-antero posterior (D1)and two orthogonal diameters in four chamber view (D2 & D3) and left atrial volume calculated by using prolate ellipse method.

Left atrial volume = (D1 X D2 X D3) X 0.523

In patients with MS in SR, LA size correlates with the development of AF, and it is recommended by ACC and AHA guidelines that those with LA size greater than 5.5 cm can be prophylactically anticoagulated. The data on left atrial size predisposing LA thrombus formation is controversial. Madden et al[5], first proposed that increased left atrial size is associated with increased risk of systemic embolism, which was supported by Sommerville and Chambers[6], who reported a three fold increase in embolism in patients with mitral stenosis with enlarged left atrial appendage on chest X-ray compared with those who did not. These observations were not supported by subsequent studies, including a multifactorial study by Peterson et al[7].

LEFT ATRIAL SPONTANEOUS ECHOCONTRAST (LASEC)

Spontaneous echo contrast (SEC) or “smoke” is characterised by discrete, dynamic, swirling smoke- like echoes, under conditions of low shear rate of flow, i.e. low velocity gradient between adjacent fluid layers.

SEC probably results from erythrocyte aggregation or rouleaux formation, while some propose a role for platelet aggregation.

Left atrial spontaneous echo contrast (LASEC), occurs in conditions that favour blood stasis, including mitral stenosis , atrial fibrillation and LA enlargement. 80% to100% of patients with LA thrombi has LASEC.

Of clinical importance LASEC is an independent predictor of thromboembolic risk in patients with MV disease, and in non valvular AF. In addition severe "smoke" showed a stronger association with LA thrombus and embolism than mild "smoke".

Analysis of SEC includes consideration of site, extent, intensity, and whether constant or intermittent. Intensity of LA.SEC is usually divided into two grades;

Marked SEC, visible at usual operative gain control of the equipment throughout the LA, and **Mild SEC**, appearing only at a high gain setting, in some portions of LA.

Though SEC is associated with increased thromboembolic risk, there is no consensus in the literature, on what therapy is indicated in patients with LA "smoke.

Patterns of blood flow in the left atrium are altered by mitral valve obstruction. Flow proximal to narrowed orifice accelerates as blood approaches the stenotic orifice, forming a high velocity jet in the orifice itself .Flow more distal to valve orifice also is altered.

ANALYSIS OF PULMONARY VENOUS DOPPLER FLOW IN MS BY TEE

Patterns of pulmonary venous Doppler flow are complex and is best visualised by TEE. As of now the pulmonary venous flow by Doppler echo, is not significantly variable between the different pulmonary veins.

Normally the pulmonary venous flow is pulsatile with forward flow in ventricular systole and diastole, followed by a backward or reversed flow during atrial systole. Forward triphasic flow pattern occurs often during normal heart rate ,with two peaks in ventricular systole viz. an early systolic , short low velocity jet (S1) (21± 17 cm/s) and a late systolic longer higher velocity jet (S 2) (55±17 cm/s).

Forward biphasic flow pattern, occurs especially during sinus tachycardia, with one peak during systole (S) and other in diastole (D).

Normal pattern of pulmonary venous forward flow , manifests peak systolic flow greater than or equal to peak diastolic flow (S > D) ,with peak systolic to diastolic flow velocity ratio > 1). Backward flow is characterised by reversal of flow during atrial systole, producing a transient, small low velocity jet (A) (17± 5 cm/s).

Pulmonary venous Doppler flow pattern is altered by MS, but conflicting data have been reported in this regard.

Keran et al[8] in 1990, analysed pulmonary venous flow in MS by TTE.

In mild to moderate MS, the systolic (S) wave was more prominent. The diastolic (D) wave, was continuous throughout to end of diastole, with a low flow shape and reduced peak velocity.. In moderate MS, marked retrograde flow into the pulmonary veins (A wave) during atrial systole was observed. In severe MS, Pulmonary vein flow is decreased during systole, (S< D) and atrial flow reversal (A) is increased, with the magnitude of these changes corresponding to the degree of elevation of left atrial pressure.

Even in sinus rhythm, the increased volume of the left atrium leads to low-velocity flow patterns, which predispose to development of atrial thrombi, particularly in the left atrial appendage.

Although the risk of left atrial thrombus formation and embolic events is thought to be low in MS patients in sinus rhythm, high prevalence of spontaneous contrast observed in TEE (upto 45% of patients)in this group raises the possibility of a higher embolic risk, even in sinus rhythm, in the presence of mitral stenosis.

Some patients in sinus rhythm have demonstrable thrombus, and in some patients with new-onset atrial fibrillation have LA thrombus suggesting thrombus formation before onset of AF.

The possible mechanism of atrial thrombus formation in sinus rhythm is the loss of atrial appendage mechanical function despite electrical evidence of sinus rhythm, leading to blood flow

stasis.

ASSESSMENT OF LEFT ATRIAL APPENDAGE (LAA) FUNCTION

Left atrial appendage is a narrow finger like space, which is elongated and having narrow base located at posterolateral aspect of heart. Its size and function

varies in different individuals. In patients with severe rheumatic MS left atrial appendage enlarges in size along with LA enlargement.

LAA function is also altered in rheumatic MS, both in sinus rhythm and in atrial fibrillation. LAA function is commonly assessed by Doppler and 2D methods.

By two dimensional multiplane transesophageal echocardiography maximal and minimal LA appendage area were measured by planimetry and LAA ejection fraction calculated using formula;

LAA EF (%) = (LAA. max –LAA .min)/LAA. max X 100

(LAA. max-Maximal LAA area (end atrial diastole), LAA. Min - Minimum area (end atrial systole)-by planimetry.)

Left atrial appendage function is assessed using pulsed Doppler imaging, with sample volume positioned at mouth of the appendage; the maximal velocity during atrial contraction is measured. This velocity is called as LAA peak emptying velocity. This velocity corresponds to the force of atrial appendage contraction or emptying.

In normal individuals ,left atrial appendage emptying velocity is greater than 50 cm/sec. Low left atrial appendage emptying velocity (<20 cm/sec) has been reported to significantly increase the embolic risk.

Significantly lower velocities occur in patients with atrial fibrillation, and this finding has been associated with a predisposition for the development of left atrial appendage thrombus and the risk of thromboembolism.

ECHOCARDIOGRAPHIC IMAGING OF LA THROMBUS

Conventional transthoracic echocardiography (TTE) has a poor yield in the detection of LA appendage thrombi. The sensitivity of TTE in detecting LA appendage clot is at the most 50 %.

The posterior location of the LA in the chest as well as due to far field and side lobe artifacts as well as use of lower frequency transducers by TTE leads to the poor visualization of the LA appendage contribute to the lack of accuracy of TTE.

On the other hand, TEE is an excellent method for detecting atrial thrombi, especially those located in the LA appendage.

This is due to use of higher frequency transducers used in TEE as well as left atrium is a posterior structure lying in near field hence producing excellent image quality.

Multiplane TEE allows imaging in numerous views thereby one can confidently diagnose or exclude LA and LA appendage thrombi.Infact TEE is 99% sensitive and 99 % specific in identifying left atrial thrombi.

Echocardiographically left atrial thrombus appear as amorphous, echogenic structure adherent to the endocardium whose appearance and texture are distinct from adjacent myocardium. They may be in variable shape and may be mobile and multiple.

An echo-lucent center may be present and it suggests that the thrombus is relatively new and actively growing.

Echocardiography can identify thrombi which are more likely to embolise. Risk factors include larger size, increased mobility, protrusion into the cavity of left atrium, heterogenous echo-density with echo-lucent center suggesting fresh thrombus.

Thrombus dimension $\geq$ 1.5 cm, history of thromboembolism and mobile thrombus were considered as predictors of subsequent embolic events.

ANTICOAGULATION IN RHEUMATIC MITRAL STENOSIS

Current recommendations for Oral anticoagulation in rheumatic MS include

Atrial fibrillation

Large left atrium > 55 mm

Left atrial thrombus

Left atrial spontaneous echo contrast

Previous embolic manifestations.

LV dysfunction EF < 0.30 %

Hypercoagulable state.

ACC and AHA recommend oral anticoagulation (INR of 2–3) in patients with mitral valve stenosis and paroxysmal or chronic atrial fibrillation and in patients with a history of systemic embolism. In patients with mitral valve disease associated with rheumatic fever, the ACCP also recommends long-term therapy with warfarin sodium (dosage adjusted to prolong the INR to 2–3) in patients who have either concurrent paroxysmal or chronic atrial fibrillation or a history of systemic embolism (e.g., stroke). Patients with rheumatic mitral valve disease and normal sinus rhythm who have a left atrial diameter exceeding 5.5 cm also should be considered for long-term anticoagulation because of their high likelihood of developing atrial fibrillation.

Patients with atrial fibrillation who have a breakthrough embolic event despite prophylactic warfarin sodium therapy should have the dosage of the drug increased (increase target INR to 3, range: 2.5–3.5) or should have aspirin (80–100 mg daily) added to therapy; another oral platelet-aggregation inhibitor (dipyridamole, clopidogrel, ticlopidine) may be used if aspirin is not tolerated.

PROBLEMS ASSOCIATED WITH ORAL ANTICOAGULATION THERAPY

Risk of hemorrhage is closely related to intensity of anticoagulation. Risk of bleeding is higher during first month and then decreases gradually owing to the fact

that prothrombin time fluctuates more initially. Other predictions of hemorrhage include poor control of

degree of anticoagulation, peripheral vascular disease, cerebro- vascular disease, and old age.

Interaction between oral anticoagulants and other drugs or foods.

Monitoring of INR.

Skin necrosis – may be seen between 3rd and 8th day of warfarin therapy, especially in patients of protein C and protein S deficiency.

In these patients, warfarin is contraindicated; the approach is long-term treatment with heparin.

In patients with severe mitral stenosis , surgical (closed mitral commisurotomy, open mitral commisurotomy or mitral valve replacement)or percutaneous interventional management (Balloon mitral valvuloplasty) are the standard mode of treatment.

In patients in whom the mitral valve is pliable (Wilkins score <8, No commissural calcium or severe sub valvular disease) management is relatively simple.

When facilities are available, Balloon mitral valvuloplasty is the treatment of choice. If expertise is not available or the cost of procedure is prohibitive, then closed mitral commissurotomy is the procedure of choice.

Closed mitral commissurotomy is a relatively simple, cheap, effective surgical procedure with low complication rate and high success rate in experienced hands.

Both the procedures needs left atrial and LA appendage thrombus ruled out by transesophageal echocardiograpy before performance.

Systemic embolization is a devastating complication that occurs 0.5 to 3.3 % of patients undergoing BMV, the major cause is LA thrombus dislodged during catheter manipulation.

The risk of this complication can be minimized by using TEE to evaluate for left atrial and appendage thrombus prior to the procedure .TEE should be performed within few days prior to the procedure, as otherwise thrombus may have formed in the interim.

If thrombus is present, the recommended approach is that the procedure should be postponed, adequate oral anticoagulation should be instituted for at least 2 to 3 weeks, and TEE repeated to

demonstrate resolution of thrombus.

If the thrombus persists, some clinicians think balloon valvuloplasty is safe if the thrombus is confined to LA appendage. However most clinicians would recommend an open surgical procedure with clot removal.

Similarly closed mitral commissurotomy cannot be safely performed if LA appendage thrombus is present, since this procedure involves introduction of finger through the LA appendage to assess the mitral valve, hence necessitating open mitral valvulotomy with clot removal.

Open mitral valvotomy carries higher surgical risk, costly and needs cardiopulmonary bypass.

Hence it seems prudent that in patients with valve anatomy suitable for BMV /CMC, a trial of oral anticoagulation may be initiated if patient is not overtly symptomatic, and look for clot resolution. If clot resolution is confirmed by TEE, these patients may be benefited by performing low risk BMV or CMC.

Only few studies[15-19] available regarding this issue .Most of the studies conclude that LA body thrombus resolution is poor and most patients need open procedure.

Many of those studies conclude that thrombus confined to LA appendage resolve with adequate anticoagulation for a period of 4 weeks to 6 months.

Our study is aimed to study the effect of oral anticoagulation on left atrial appendage thrombus resolution in our population and to analyse various factors associated with resolution or reduction in size of left atrial appendage thrombus.

ACITROM-ACENOCOUMAROL –Is the oral anticoagulant used in this study. It is the oral anticoagulant widely available and commonly used drug in our institution.

Its action as well as side effect profiles are similar to warfarin sodium .It acts by inhibiting Vitamin K reductase enzyme, thereby prevents activation of Vitamin K which in turn is essential for activation of Vitamin K dependant coagulation factors involved in coagulation cascade,

thereby exhibiting anticoagulant action

MECHANISM OF ACTION OF WARFARIN

The vitamin K cycle and its link to carboxylation of glutamic acid resides on vitamin K dependant coagulation proteins. Vitamin K1 obtained from food sources is reduced to vitamin KH2 by a warfarin resistant vitamin K reductase. Vitamin KH2 is then oxidized to vitamin epoxide (vit KO) in a reaction that is coupled to carboxylation of glutamic acid residues on coagulation factors.

This carboxylation step renders the coagulation factors II, VII, IX, and X and the anticoagulant factors protein C and proteins functionally active. Vit KO is then reduced to vit K1 in a reaction catalysed by vitamin KO reductase. By inhibiting vitamin KO reductase, warfarin blocks the formation of vitamin K1 and vitamin KH2, thereby removing the substrate (vitamin KH2) for the carboxylation of glutamic acid.

Vitamin K1, either given therapeutically, or derived from food sources can overcome the effect of warfarin by bypassing the warfarin sensitive vitamin KO reductase step in the formation of vitamin KH2.

REVIEW OF LITERATURE

The predictors of thromboembolism in MS , is the present focus of interest , There is no correlation in MS , between the risk of embolism and NYHA functional cardiac status , MV area , MV calcification , and duration of AF.

The tendency for embolisation in MS correlates directly with the age of the patient, size of the LAA, and indirectly with the cardiac output. MS patients more than 35 years of age, with dilatation of LAA, and with low cardiac output are at the highest risk of emboli. In a recent retrospective generalized study with TEE, it was observed that MS, LA dilatation and severe left ventricular dysfunction , are independent risk factors for LAA thrombus formation. In addition, atrial fibrillation and left atrial spontaneous echo contrast have been associated with increased risk of cardiogenic embolism in MS

Gaswami et al[9] prospectively investigated various clinical and echocardiographic variables to predict the left atrial and left atrial appendage clot and spontaneous echo contrast in patients with severe rheumatic mitral stenosis. They studied 200 consecutive patients (112 males and 88 females; mean age 29.6±9.6 years). Left atrial clot and spontaneous echo contrast were present in 26 and 53.5% of cases, respectively. There were no significant differences in the mitral valve area, mean transmitral diastolic gradient and left ventricular ejection fraction between patients with and without clot.

Patients with clot were older (34.4±11.4 vs. 28.2±8.5 years, P<0.001), had longer duration of symptoms (41. 4±36.0 vs. 28.8±22.9 months, P<0.001), more frequent atrial fibrillation and spontaneous echo contrast (69.2 vs. 16.9%, P<0. 00001 and 76.9 vs. 45.3%, P<0.00001, respectively) and larger left atrial area and diameter (41.0±12.7 vs. 29.9±7.4 cm(2), P<0.00001 and 53.9±8.3 vs. 47.6±7.4 mm, P<0.0001, respectively) as compared to patients without clot. Similarly patients with

spontaneous echo contrast were older (31±10.4 vs. 27.8±8.3 years, P<0.01), had more frequent atrial fibrillation (48.6 vs. 9.7%, P<0.0001), left atrial clot (37.4 vs. 12.9%, P<0.0001), larger left atrial area and diameter (37.6±11.2 vs. 28.1±6.7 cm(2), P<0.00001 and 52.2±8.3 vs. 45.9±6.5 mm, P<0.00001, respectively) and smaller mitral valve area (0.77±0.14 vs. 0.84±0.13 cm, P<0.01) as compared to patients without spontaneous echo contrast.

There were no significant differences in the mean transmitral diastolic gradient and left ventricular ejection fraction. On multiple regression and discriminant function analysis, atrial fibrillation and left atrial area were independent predictors of left atrial clot formation. In a subgroup of patients with sinus rhythm, larger left atrial area and presence of spontaneous echo contrast were significantly associated with the presence of clot in left atrium and appendage.

They concluded that in patients with severe mitral stenosis, the presence of atrial fibrillation and in the subgroup of the patients with sinus rhythm the presence of large left atrium (> or =40 cm and spontaneous echo contrast were associated with higher risk of clot formation in the left atrium and might be benefited by prophylactic anticoagulation.

Gonzalez-Torrecilla E et al[10] investigated the independent factors associated with the presence of left atrial (LA) spontaneous echo contrast (SEC) and thromboembolic events in patients with mitral stenosis (MS) in chronic atrial fibrillation (AF) Transesophageal and transthoracic echo studies were performed in 129 patients with MS in chronic AF. Previous embolic events were documented in 45 patients, 20 of them within 6 months, and 65 patients were receiving long-term anticoagulation. The intensity of LASEC and mitral regurgitation, the presence of thrombi and active LA appendage flow (peak velocities > or = 20 cm/s), and LA volume as well as other conventional echo-Doppler determinations were investigated in every patient. The prevalence of significant LASEC (degrees 3+ and 4+), thrombus, active LA appendage flow, and significant mitral regurgitation (>2+) were: 52% (67 patients), 29.5% (38 patients), 32% (41 patients), and 36% (47 patients), respectively.

Multivariate analysis showed that decreasing mitral regurgitation severity, absence of active LA appendage flow, and mitral valve area were the independent correlates of LASEC (odds ratio [OR] 3.7, 5.4, and 0.17, respectively; all $p < 0.02$). Active LA appendage flow and anticoagulant therapy were associated negatively, whereas the severity of LASEC was associated positively with the finding of LA thrombus (OR 9.6, 3.9, and 1.6, respectively; all $p < 0.05$). The intensity of LASEC and previous anticoagulant therapy (OR 1.74 and 4.5, respectively; $p < 0.005$) were the independent covariates of thrombi and/or recent embolic events.

In conclusion, the severity of mitral regurgitation and lack of active LA appendage flow were, respectively, the strongest independent correlates of significant LASEC and thrombus in patients with MS in chronic AF. LASEC remains the cardiac factor most strongly associated with thrombus and/or recent embolic events in these patients.

Acarturk E et al[11] studied the thromboembolism risk in patients with mitral stenosis.They evaluated a total of 168 consecutive patients with predominant rheumatic mitral stenosis by transthoracic (TTE) and transesophageal echocardiography (TEE). Of the 168 patients, 35 had previous embolic events (group I) and 133 had no emboli (group II). A total of 77 (45.8%) patients had atrial fibrillation. The frequency of atrial fibrillation was higher in group I than group II (68.6% vs. 39.8%, $p < 0.001$). The incidence of left atrial enlargement was greater in group I ($p < 0.001$). Mitral valve area was found to be smaller in group I compared to group II ($p < 0.001$). In group I 83.3% and 29.2% of the patients with atrial fibrillation had left atrial spontaneous echo contrast (SEC) and left atrial thrombus, respectively, and 72.7% of the patients with sinus rhythm had left atrial SEC. In group II 79.2% and 20.8% of the patients with atrial fibrillation had left atrial SEC and left atrial thrombus whereas 28.6% and 2.6% of the patients with sinus rhythm had left atrial SEC and left atrial thrombus, respectively.

The incidence of left atrial thrombus was significantly different in those patients with compared to those without embolic events (20% vs. 9.7%, $p < 0.01$).

In groups I and II, 28 of 35 (80%) and 64 of 133 (48.1%) patients had left atrial SEC ($p < 0.01$). Patients with left atrial SEC had a greater left atrial size ($p < 0.01$) and smaller

mitral valve area ($p < 0.01$). Left atrial size was normal in 2 patients with left atrial SEC and SEC was not found in 55 patients with enlarged left atrium. Multiple logistic regression analysis showed that atrial fibrillation, mitral valve area and left atrial enlargement were independent predictors of the SEC ($p < 0.001$) and left atrial SEC was the principal determinant of thromboembolism.

They concluded thatt that regardless of rhythm and atrial size, left atrial SEC is a principal determinant of thromboembolic risk in mitral stenosis and suggested that TEE may be able to detect those patients with mitral stenosis at risk for emboli and guide appropriate therapy

S J Saidi et al[12] **studied the** incidence and factors influencing left atrial clot in patients with mitral stenosis and normal sinus rhythm. In their study, no meaningful relation was found between left atrial size and the presence of a clot in the left atrium, or between age and clot formation. On the other hand, despite the fact that the mean mitral valve score in the MS group in NSR with a clot was higher than the group without a clot, the difference was not significant. Another result of this study was the comparison of clot frequency in patients in NSR with those in AF rhythm. Clotting was more common in the AF group, with the difference being significant, as could be expected. Age of the patients in AF rhythm in that study was significantly higher than the group in NSR.

Concerning the left atrial size, mitral valve score and valve gradient, obtained values were significantly higher in the AF group compared to the group in NSR. Also concerning the coexistence of

MR with MS and its effect on inhibiting clot formation, their study showed a lower percentage of clotting in the combined pathology (MS and MR) group compared to the pure MS group, although the difference was not significant. This could be because the MR present in the majority of the patients in this study was of mild severity.

They concluded that despite the fact that left atrial clot is usually sought in MS patients with AF rhythm; MS patients in NSR are also at risk from intra-atrial clot formation. Although this risk is less than the AF rhythm group, it is sufficient to warrant measures for prevention of thromboembolic episodes in this group of patients.

Leung et al[13] performed transesophageal echocardiograms in 2.894 patients over a 6.5 year period. They found 94 patients (3.2 %) to have left atrial thrombus. The thrombi were considered as mobile in 45 patients .Seventeen patients had suffered from a stroke or embolic event (event rate: 10.4% per year) and 27 had died (mortality: 15.8% per year) during a follow-up period of 19.2 months.

Thirty-three patients had thrombus with a maximum dimension ≥ 1.5 cm. Thrombus dimension≥ 1.5 cm, history of thromboembolism and mobile thrombus were considered as predictors of subsequent embolic events.

ORAL ANTICOAGULATION IN LEFT ATRIAL APPENDAGE THROMBUS

Only limited literatures are available which studied the effect of oral anticoagulation on left atrial thrombus resolution. Most of the studies suggest left atrial body thrombus resolves poorly with oral anticoagulation .Left atrial appendage thrombus resolves variably in different studies. The standard treatment for left atrial thrombi once identified is anticoagulation with heparin and/or warfarin. The rational of anticoagulation therapy is to prevent further increase of existing thrombi and emboligenic material formation on the surface of an existing thrombus.

Silaruks S et al[14] studied the resolution of left atrial thrombus after 6 months of anticoagulation in candidates for percutaneous transvenous mitral commissurotomy .They have used oral warfarin sodium for 219 potential candidates for percutaneous mitral commissurotomy (PTMC) with left atrial thrombus (mean age 39.6 (7.4) years).Complete resolution of thrombus was demonstrated in 53 patients (24.2%), who subsequently underwent successful PTMC. In another 166 patients, the thrombus size was reduced by 24% ($p < 0.001$) .No thrombus resolution was observed in the 27 patients with a left atrial body thrombus. Eighteen patients had minor bleeding.

The significant predictors of thrombus resolution were a New York Heart Association functional class ⩽ II, a left atrial appendage thrombus size ⩽1.6 cm^2,

a left atrial spontaneous echocardiographic contrast grade of ⩽1, and an international normalised ratio (INR) of at least 2.5. Patients with all of these predictors had a 94.4% chance of complete thrombus resolution (95% CI 84.4% to 98.1%).

Jaber WA et al[15] similarly studied efficacy of anticoagulation in resolving left atrial and left atrial appendage thrombi by using transesophgeal echocardiography, concluded that a significant number of patients with LA appendage thrombus undergo resolution over long term anticoagulation.

Corrado et al[16] concluded that the anticoagulation therapy was associated with resolution of atrial thrombi in the majority (81.8%) of patients presented with atrial fibrillation of recent onset.

Kandpal et al[17]. showed that 41.7% of isolated LA appendage clots resolved in contrast to 12.5% of LA body clots in patients with mitral stenosis after 6months of oral anticoagulation.

Recently **J Srimannarayana et al**[18] studied the occurrence of left atrial body and left atrial appendage clots in patients with rheumatic mitral stenosis and atrial fibrillation, and to document the effect of long-term anticoagulation on clot dissolution.

They selected consecutive patients with severe rheumatic mitral stenosis and atrial fibrillation and they were assessed by transesophageal echocardiography. Those with left atrial body or left atrial appendage clots were anticoagulated with oral nicoumalone.

Transesophageal echocardiography was then repeated in patients on anticoagulation who were on regular follow-up, and in whom percutaneous transvenous mitral commissurotomy could be considered. Of the 490 patients studied, 163 had left atrial body or left atrial appendage clots. A repeat transesophageal echocardiographic examination was done in 50 patients who had optimal anticoagulation for a period of 6 months. Only 2 of the 17 patients who had left atrial body clots had successful clot dissolution after long-term anticoagulation, while the left atrial appendage clots disappeared in 31 of 33 patients ($p<0.001$).

They concluded that left atrial clots are present in a third of patients with severe rheumatic mitral stenosis and atrial fibrillation and isolated left atrial appendage clots in patients with rheumatic mitral stenosis and atrial fibrillation can disappear with long-term anticoagulation, while thrombi that extend into the left atrial body may persist despite optimal anticoagulation.

Murillo et al[19]**.** showed that PTMC can be performed in patients with an LA appendage clot with TEE guidance and fluoroscopic control. However, this can be fraught with the risk of embolism. Hence, the interventional cardiologist will always prefer the LA and LA appendage to be free of clots before embarking on balloon mitral valvotomy.

STUDY DESIGN AND METHODOLOGY

This study was performed in the year 2005 in the Department of Cardiology, Madras Medical College and Government General Hospital, Chennai.

INCLUSION CRITERIA

1. Patients with severe isolated mitral stenosis with valve anatomy suitable for PTMC/CMC

2. No significant lesions in other valves (mild or less only selected) except for Tricupid regurgitation secondary to Pulmonary hypertension.

3. NYHA Class I-III status.

4. Patients newly started oral anticoagulation, with no significant oral anticoagulation previously.

EXCLUSION CRITERIA

1. Patients with NYHA class IV status.

2. Moderate to severe calcification of mitral valve

3. Left atrial body thrombus.

4. Significant other valve involvement (more than mild) including significant mitral regurgitation.

5. Significant co-morbid conditions.

6. Previous cardiac surgery including closed mitral commissurotomy.

7. Pregnancy and puerperium.

8. Those patients who did not give consent for the study.

Sixty patients who met the inclusion criteria are screened for left atrial appendage thrombus by TEE. Thirty patients with severe mitral stenosis who

showed evidence of left atrial appendage thrombus by transoesophageal echocardiography and who gave consent for the study were selected for the study. Five patients who lost follow-up were excluded from the study.

Informed consent was obtained from all the patients after explaining the study.

A thorough history including NYHA status of breathlessness, orthopnoea, PND, H/O thromboembolism, peripheral oedema, chest pain, palpitations, haemoptysis and previous treatment details were obtained.

Complete physical examination was done in all patients. A 12 lead electrocardiogram and chest X-ray were taken routinely. Repeat ECGs were taken as and when needed.

The study group included 25 patients (16 female and 9 male) aged between 22 to 44 years (mean 32.2 yrs).All patients had definite evidence of left atrial appendage thrombus by TEE.

20 patients were in atrial fibrillation (including 3 patients in intermittent atrial fibrillation) and 5 patients were in sinus rhythm during the study.

ECHOCARDIOGRAPHIC DATA

A complete Transthoracic echocardiogram was obtained including M- mode, 2D, colour Doppler and pulse& continuous wave Doppler in every patient.

ALOKA Trivitron model echo machine was used for this study. A 2.5 MHZ probe was used for transthoracic echocardiography and a 5 MHZ multiplane probe was used for transesophageal echocardiography.

Lesion severity in individual valve was characterised by various methods.

Specific attention was paid in assessing mitral valve morphology, Wilkin's scoring, mitral valve area by planimetry & pressure half time method, peak and mean transmitral gradient.

M-mode echocardiogram with cube formula was used to assess global LV systolic function. M-mode echocardiogram at mitral & aortic valve level was obtained routinely for measurement.

Left atrial dimensions were measured in end systole in PLAX- antero posterior (D1)and two

orthogonal diameters in four chamber view(D2 &D3) and left atrial volume calculated by prolate ellipse method.

Left atrial volume = (D1 X D2 X D3) X 0.523

A note on spontaneous echo contrast in left atrium was made. Its severity graded as

Grade 1-Mild, Grade 2 –Marked.

Left atrial appendage was visualised in PSAX view at aortic valve level and LAA thrombus is characterized by measuring its major and minor dimensions. A focused transoesophageal echocardiogram was obtained for all patients.

Multiple views were used to visualise the entire left atrium for identifying evidence of thrombi by TEE.

Left atrial appendage was visualised thoroughly in multiple planes. LA appendage was examined in at least two orthogonal views .A basal short axis view at approximately 45 * and a more vertical plane 90-120 * with leftward rotation of probe were used to visualise it.

Care was taken to distinguish normal trabeculation from localised thrombus formation. Trabeculae tend to be more linear and are continuous with the atrial wall in

more than one view. Thrombi typically protrude into the appendage, often with independent motion.

Once visualised thrombi is assessed for size, mobility and whether it extends to body of the left atrium. Size of the thrombus is measured as major and minor dimensions.

LA appendage area in diastole & systole were measured and LAA ejection fraction calculated using formula;

LAA EF (%) = (LAA.max –LAA .min)/LAA. max X 100

(LAA.max-Maximal LAA area (end atrial diastole), LAA.Min.- Minimum area (end atrial systole)- by planimetry.)

Left atrial appendage function was assessed using pulsed Doppler imaging, with sample volume positoned at mouth of the appendage; the maximal velocity during atrial contraction was measured. This velocity corresponds to the force of atrial appendage contraction or emptying.

Pulmonary venous pulsed wave Doppler was obtained from left upper lobe pulmonary vein. Entire left atrium was searched for thrombus and specific note was made on mitral valve morphology and left atrial spontaneous echo contrast.

All patients received standard medical treatment with, Digoxin, Penicillin, Pottasium chloride syrup, Verapamil, Diuretics and other drugs according to the clinical condition.

Oral anticoagulation started in all patients with 2 -3 mg of Acitrom(Acenocoumorol) once daily. Dose adjustments were made weekly by monitoring Prothrombin time and INR (International normalised ratio).

INR was maintained between 2-3. Patients were followed up weekly by monitoring any symptom change, bleeding, thromboembolic episode, and prothrombin time and INR measured. Fresh ECGs were taken when clinical suspicion of change in rhythm was noted.

Oral anticoagulation was continued for 6 weeks..

Focussed transthoracic and transesophageal echocardiogram was repeated after 6 weeks and the important parameters were collected. Left atrial appendage thrombus presence/absence, and if LAA thrombus was present, its size in major and minor dimensions were measured in both TTE and TEE.

A note on LA spontaneous echocontrast was made.

All the data collected were subjected to statistical analysis and conclusion derived.

STATISTICAL ANALYSIS

Continuous variables were expressed as mean values with standard deviation, while proportions were presented as numbers and percentages of the total. The significance of differences between means

was tested by the Student's t test, while that between proportions was tested with the Chi-square test. A p value <0.05 was considered significant.

OBSERVATIONS AND RESULTS

This study involved twenty five patients (16- female; 9- male) aged between 22 to 44 years (Mean 32.2 ± 6.4 years).Among these patients 17 patients were in atrial fibrillation and 5 patients remained in sinus rhythm throughout the study. Three patients who were in AF during start of the study showed intermittent sinus rhythm during follow-up.

All the patients had severe mitral stenosis with mean mitral valve area by pressure half time method was 0.62 ± 0.11 sq.cm and mean and peak gradient 15.4±1.95 and 24.65 ± 2.98 mm Hg.. Mitral regurgitation was mild in 14 patients and trivial in 11 patients.

None of the patients had significant aortic valve disease (3-patients had mild aortic stenosis and 8-patients had mild aortic regurgitation).None of the patients had significant tricuspid stenosis. Tricuspid regurgitation secondary to pulmonary hypertension was present in all patients .7 patients had severe TR, 5 patients had moderate TR and remaining 13 patients had mild TR. Pulmonary hypertension secondary to mitral stenosis was severe in 10 patients and moderate in 12 patients and mild in 3 patients.

The Wilkin's score ranged between 5 to 9 with Mean ± SD was 7.32±1.1. Left atrial dimension in parasternal long axis at aortic valve level was 5.86 ±0.56 cm. LA volume calculated by prolate ellipse method was 151.05 ±40.27 ml.

All patients showed evidence of left atrial spontaneous echo-contrast (LASEC).Eleven patients were graded to have Mild LASEC and fourteen patients had ble change in the marked LASEC. LA appendage was dilated in all patients with maximum area by planimetry method ranged between 3.8 cm ^{2} to 7.35 cm ^{2,} mean± SD (5.32 ±0.77 cm^{2}).

Average LA appendage ejection fraction was 19.20±8.4 % in the study group and markedly differed between sinus rhythm group and atrial fibrillation group. In sinus rhythm LAA ejection

fraction was 31.52± 7.9 % and in those with AF it was 16.1± 5.13%. LA appendage emptying velocity ranged between 7 cm /sec to 50 cm/sec with mean ± SD 17.9± 11.7 cm/sec, which also differed significantly between two groups .In atrial fibrillation group LAA-EF was 12.63±4.95 cm/sec and in sinus rhythm group it was 39 ± 2.6 cm/sec.

LA appendage thrombus was present in all patients. Their major and minor dimensions ranged between 1.2x1.1 cm to 4.7 x 2.1 cm.

The dose of Acitrom needed ranged between 2 to 4 mg / daily, and all patients were maintained with INR 2 to 3 over a mean period of 3 weeks. None of the patients reported significant symptom change or any history suggestive of thromboembolic episode during 6 weeks follow-up.On serial ECGs 3 patients showed sinus rhythm intermittently. All of them were in atrial fibrillation on 6th week .

Focussed TEE done at 6th week showed complete resolution of LA appendage thrombus resolved in four patients and more than 30% reduction in size of thrombus in four patients. In the remaining 17 patients there were no significant changes in the size of the thrombus. None of the patients showed significant increase in size of the thrombus.

Repeat objective reassessment of left atrial spontaneous echo-contrast was done. None of the patients showed any notagrade of LASEC

BASELINE CHARECTERISTICS

Characteristics	Number
Sex	
Male	**9**
Female	**16**
Age group	
<30 yrs	**6**
30-40 yrs	**15**
>40 yrs	**4**
Rhythm	
SR	**5**
AF	**17**
Intermittent AF	**3**
MR	
Trivial	**14**
Mild	**11**
PHT	
Mild	**3**
Moderate	**12**

Severe LASEC Grade	**10**
Mild(I)	**11**
Marked(II)	**14**

BASELINE CHARACTERISTICS

Baseline Characteristics	Mean± SD
Mitral valve area (cm^2)	0.62±0.11
LA dimension(PLAX) (cm)	5.86±0.56
LA volume (ml)	151.06±40.27
Mean gradient (mm Hg)	15.4±1.95
Peak gradient (mm Hg)	24.65±2.98
Wilkin's score	7.32±1.1
LAA area-Maximum (cm^2)	5.32±0.77
LAA-Ejection fraction (%)	
Over all	19.20±8.4
LAA -EF-In SR	31.52±7.9
LAA-EF-In AF	16.12±5.1
LAA-emptying velocity(cm/sec)	
Over all	17.9±11.7
In SR	39±2.6
In AF	12.63±4.95

RESULTS

Resolution of Left atrial appendage thrombus occurred in 16% (4) of the individuals. Reduction in size of more than 30%was seen in 16% (4) patients.

Remaining 68% (17) of the patients showed no significant change in thrombus size. None of the patients showed significant symptom change or thromboembolic episode or any bleeding. No significant change in grading of LASEC was noted in any of the patients.

SUB GROUP ANALYSIS

LAA thrombus resolution or reduction in size occurred in 66.6% of patients in the age group of <30 years and in 26.6% of patients in the age group of 30 to 40 years. None of the patients above 40 years of age had any resolution or reduction in size of the thrombus. The mean age of patients who showed complete resolution was 27.25 years as against 34.05 years in patients with no resolution.

Similarly 60% of patients in sinus rhythm and 66.6 % of patients with intermittent AF showed resolution or reduction in size of the study. But only 11.6% of patients with atrial fibrillation showed resolution or reduction in size and 88.4% of patients with atrial fibrillation showed no or minimal change in thrombus size.

All the patients who showed complete thrombus resolution had thrombus dimension less than 1.5 cm in major axis. Among the patients with thrombus dimensions > 1.5 cm size, none of them showed complete resolution and only 13.3% showed significant reduction in size.

There is no significant difference in mitral valye area among the three groups. Mean Wilkin's score was significantly lower in patients who had thrombus resolution as against those without resolution (6.5 vs 7.47).Patients showing no change in thrombus dimension had significantly higher left atrial dimensions and volume.

Patients who showed resolution of thrombus had significantly higher LAA ejection fraction compared with those showing no change in thrombus dimensions. (28 ± 0.12 vs

15.86 ± 0. 06)

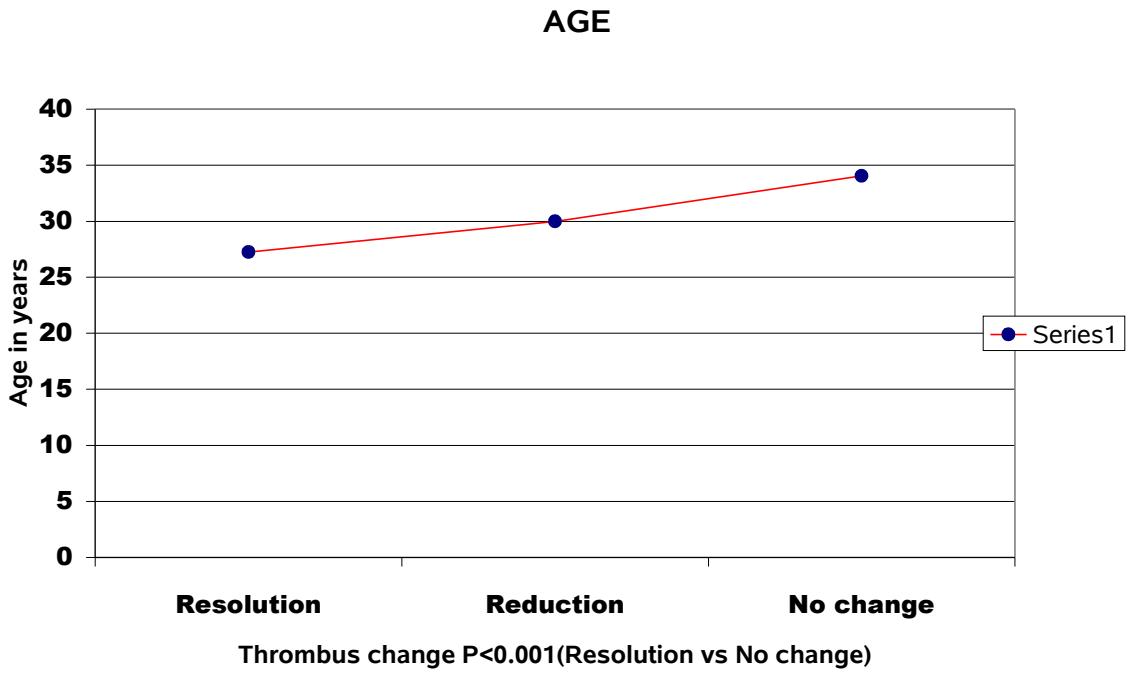
Similarly patients who had resolution of thrombus had significantly higher LAA peak emptying velocity compared with those without any change. (32.5 ± 14.1 cm/sec. vs 12.45 ± 5.96 cm/sec.)

RESULTS

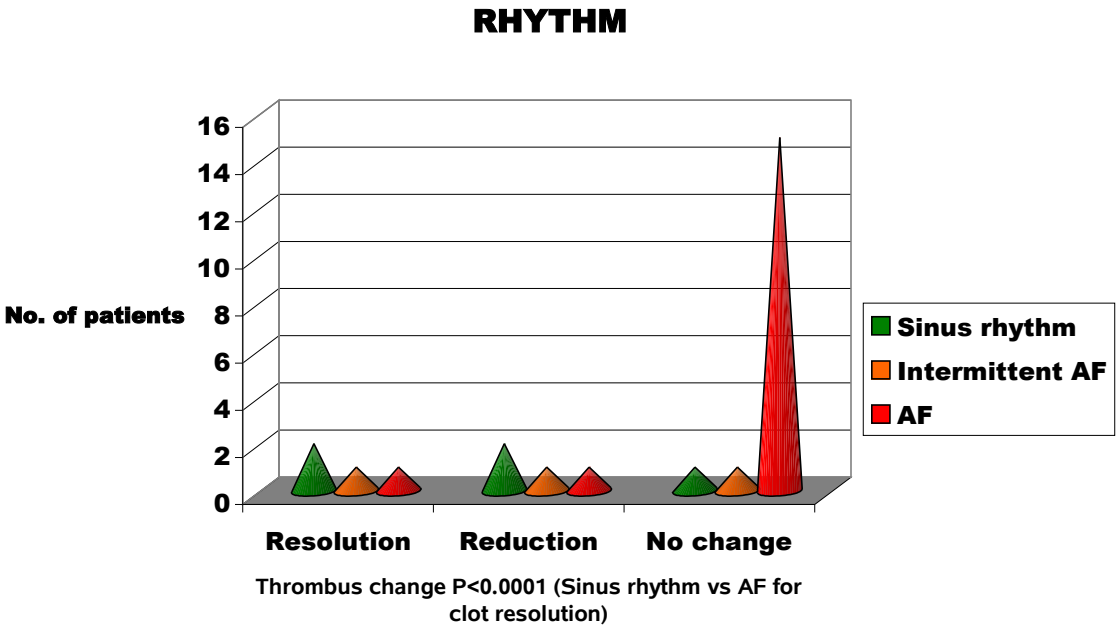
	Age(yrs)			Rhythm			Clot Size(major dimension)		LAA Emptying Velocity	
	<30 (6)	30-40 (15)	>40 (4)	AF (17)	AF-I (3)	SR (5)	<1.5cm (10)	>1.5cm (15)	<30 cm/s (19)	>30 cm/s (6)
Resolution	(2) 33.3%	(2) 13.3%	(0)	(1) 5.8%	(1) 33.3 %	(2) 40%	(4) 40%	(0)	(0)	(4) 66.6%
>30% Size Reduction	(2) 33.3%	(2) 13.3%	(0)	(1) 5.8%	(1) 33.3%	(2) 40%	(2) 20%	(2) 13.3%	(2) 10%	(2) 33.4%
No / Minimal Change	(2) 33.3%	(11) 73.3%	(4) 100%	(15) 88.4%	(1) 33.3%	(1) 20%	(4) 40%	(13) 88.7%	(17) 90%	0

SUB GROUP ANALYSIS

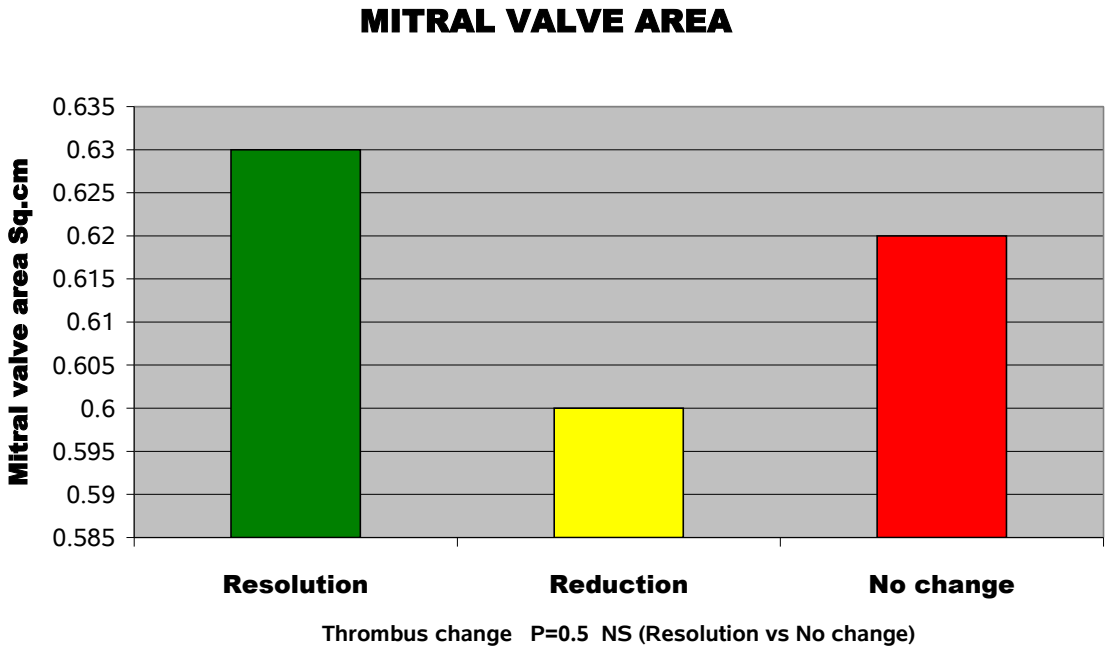
Characteristics	Resolution	Reduction	No change	P value (Resolution vs No change)
Age(Yrs)	27.25±6.4	30±7.6	34.05±5.6	< 0.001
Sex				
Male	2	1	6	0.1
Female	2	4	10	NS
Rhythm				SR vs AF
SR	2	2	1	
AF	1	1	15	<0.0001
AF-I	1	1	1	
Wilkins's score	6.5±1	7.5±1.29	7.47±1.06	<0.01
LA dimension(cm)	5.67±0.68	5.6±0.59	5.97±0.52	<0.01
LA volume(ml)	138.95±56.2	146.25±26.0	155.05±39.9	<0.02
LAA-EF(%)	28±0.12	24.93±0.05	15.86±0.06	<0.001
LAA empt. Vel.(cm/sec)	32.5±14.1	26.5±14.66	12.45±5.96	<0.001
Mitral valve area	0.63±0.12	0.60±0.12	0.62±0.1	0.5 NS
Thrombus size				<0.0001
Less than 1.5 cm	4	2	4	
More than 1.5 cm	0	2	13	



The chance of clot resolution reduces with age

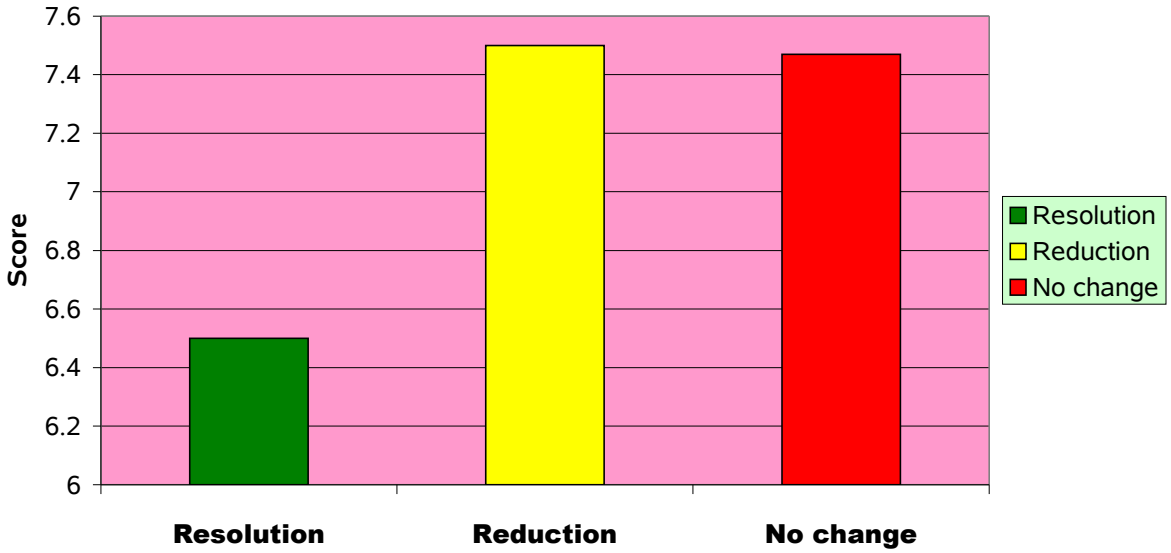


Sinus rhythm favours thrombus resolution, whereas persistant AF is associated with poor resolution



There is no significant correlation between mitral valve area and resolution of LA thrombus.

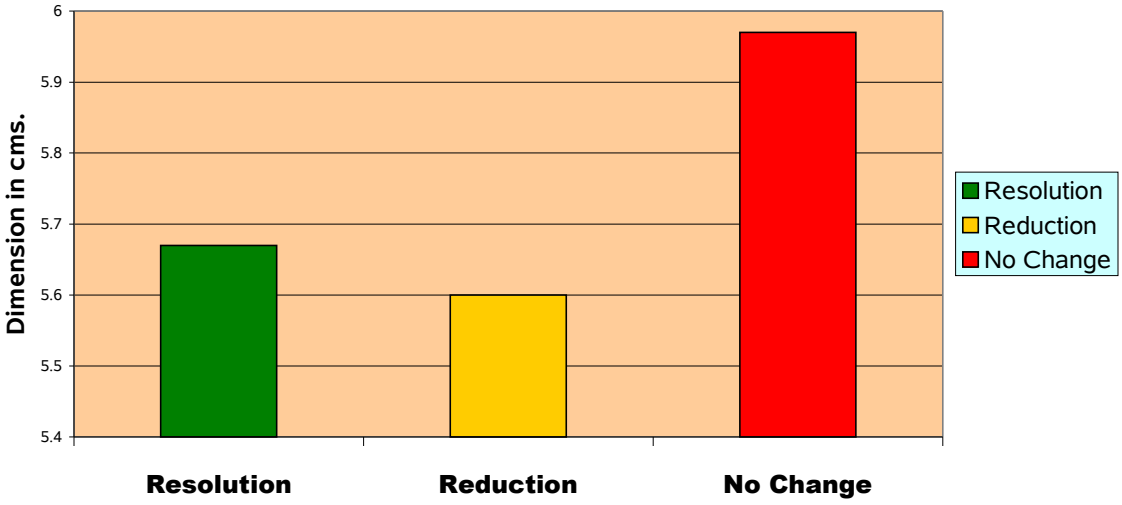
WILKIN'S SCORE



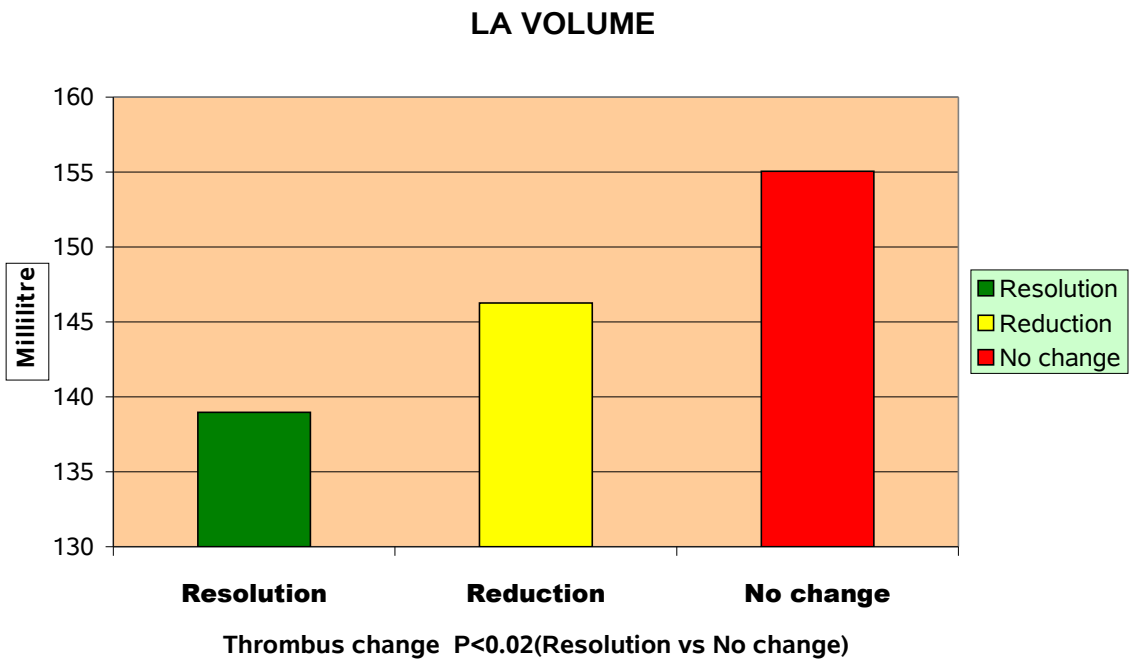
Thrombus change P<0.01(Resolution vs No change)

Higher Wilkin's score is associated with lower clot resolution

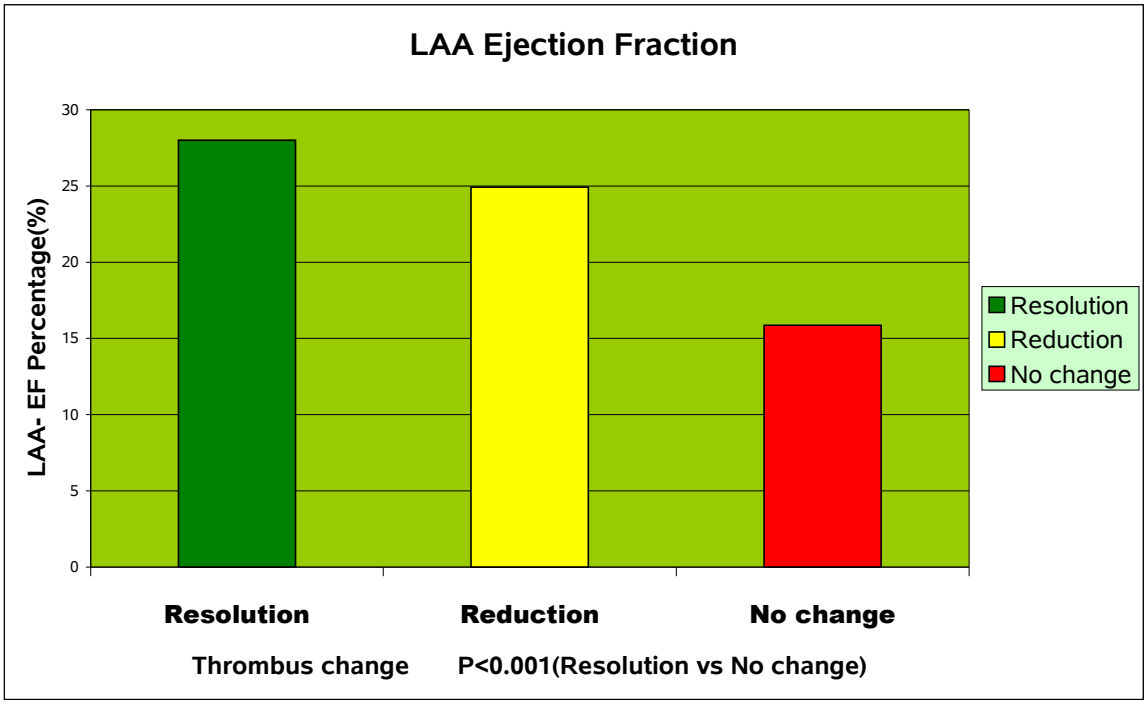
LA Dimension (cm)



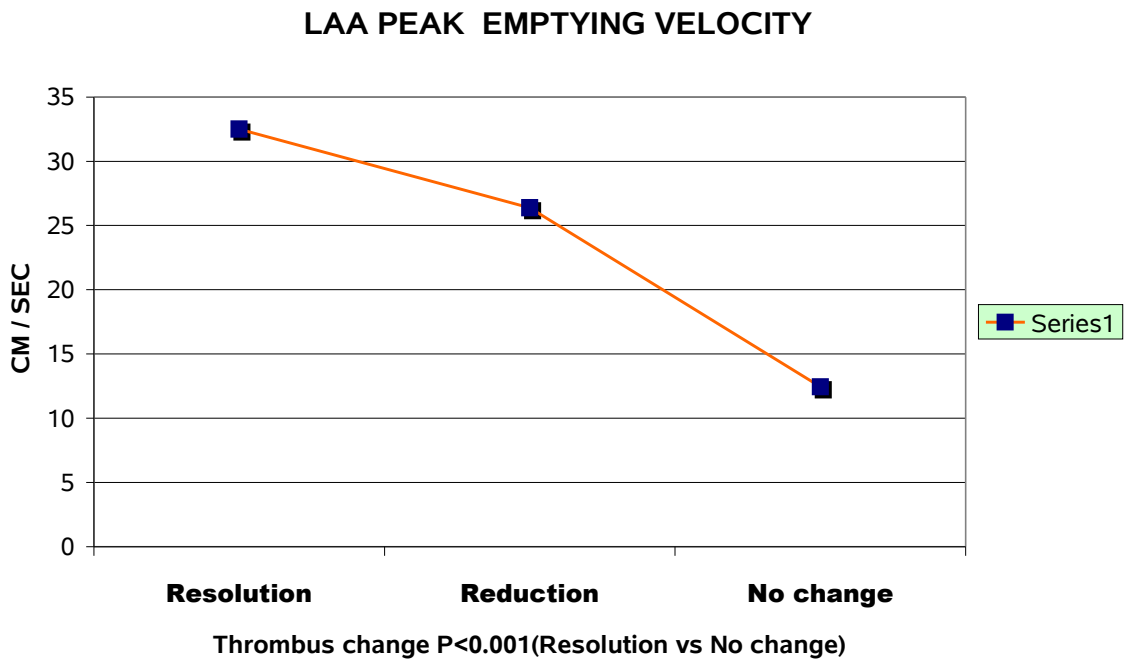
Thrombus change p < 0.01 (Resolution vs No change)



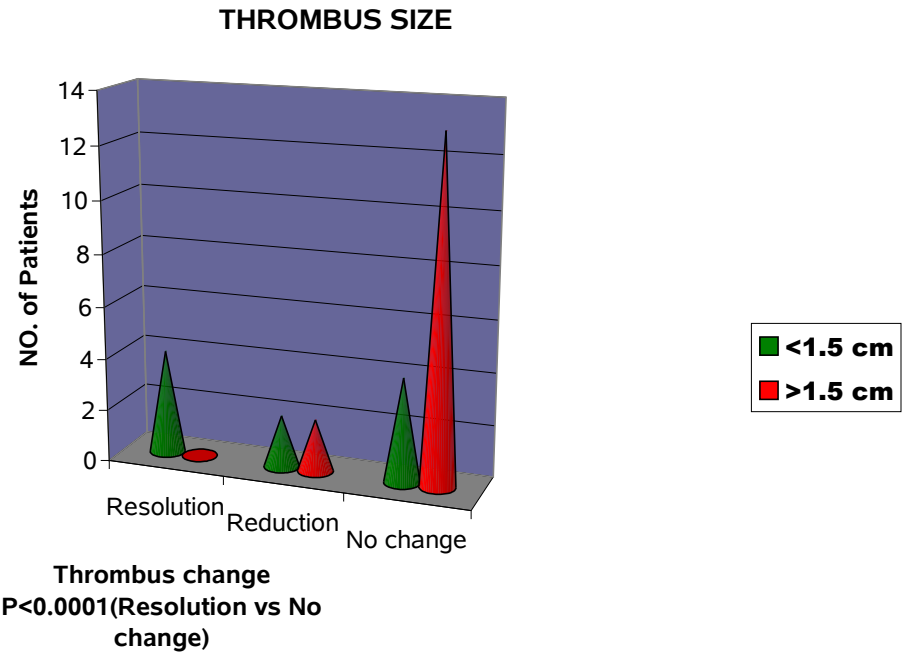
LA dimensions and volume were significantly larger in those with no resolution compared with those resolution.



Patients who showed thrombus resolution had significantly higher LAA –EF compared to those who did not any change.



Reduction in LAA peak emptying velocity was associated with reduction or failure of thrombus resolution



Thrombus size significantly influences resolution. Those with < 1.5 cm size resolves rapidly as against those with size > 1.5 cm, which were associated with poor resolution

DISCUSSION

Anticoagulation is conventionally used to reduce the risk of the thromboembolic events associated with AF. Oral anticoagulants act by inhibiting the synthesis of vitamin K-dependent coagulation factors. This prevents new thrombus formation, and promotes adherence and organization of old thrombi to the surrounding endocardium.

However, recent studies have supported an alternative hypothesis of benefit that includes not only the prevention of new thrombus formation but also the resolution of existing thrombi.

In situations in which a thrombus is already present, anticoagulation prevents further thrombus extension, thereby facilitating the action of endogenous fibrinolysis.

A study conducted by Kandpal et al. showed that 41.7% of isolated LA appendage clots resolved in contrast to 12.5% of LA body clots in patients with mitral stenosis after 6 months of oral anticoagulation. Resolution of atrial thrombi after oral anticoagulation in patients with non- valvular AF has also been examined in several studies.

In the present study, we have analyzed factors associated with resolution of LA appendage thrombus with oral anticoagulation.

Older age (>40 years) was not only associated with increased prevalence of left atrial thrombus but also with failure of thrombus resolution with anticoagulation.

Similarly presence of atrial fibrillation favors stasis and abnormal low velocity flow patterns in the left

atrium and appendage associated with failure of thrombus resolution. Left atrial appendage peak emptying velocity and LAA ejection fraction were significantly lower in patients with atrial fibrillation and are associated with failure of thrombus resolution.

On the other hand patients with sinus rhythm had significantly higher LAA peak emptying velocity and LAA ejection fraction and associated with better resolution or reduction in thrombus size.

From the above observations it seems prudent that intact mechanical function of left atrial appendage facilitates the action of oral anticoagulants on the thrombus and resulting in resolution.

Patients with smaller thrombus size (<1.5 cm) showed better resolution compared with larger thrombus size. This difference is possibly explained by the fact that a higher thrombus burden does not permit dissolution with endogenous fibrinolysis despite optimal anticoagulation and with much smaller thrombus burden, allows dissolution by endogenous fibrinolysis, while effective oral anticoagulation prevents fresh thrombus formation.

From the above observations a management strategy can be derived. Stable patients with isolated severe mitral stenosis whose valve anatomy is suitable for balloon mitral valvulotomy with isolated left atrial appendage thrombus can afford to be on adequate oral anticoagulation for a short period (6weeks to 6 months) if the thrombus is small especially if they are young and in sinus rhythm. If repeat TEE revealed thrombus resolution they can be subjected to balloon mitral valvotomy or closed mitral commissurotomy.

If the thrombus does not resolve they can be referred for open surgical procedure.

On the other hand, older patients and those with large LA appendage thrombus or LA body thrombus

can be straightaway referred for open surgical procedure with clot removal

LIMITATIONS OF THE STUDY

This is a small non randomised study involving small number of selected patient group. The patient groups are treated for shorter period of time. Further, large-scale study with longer duration (6 months) of follow up may be necessary to confirm the findings of our study.

CONCLUSION

Adequate oral anticoagulation (INR 2-3) is effective in resolution of left atrial appendage thrombus in rheumatic mitral stenosis in a significant group of patients over a period of six weeks. The resolution is either complete or partial.

Among patients receiving oral anticoagulation, 16% showed complete resolution of thrombus and another 16% showed more than 30% reduction in size of thrombus.

Factors associated with resolution or reduction in size include

Younger age (<40 years)

Small thrombus size (< 1.5 cm)

Sinus rhythm,

Intermittent atrial fibrillation

Left atrial appendage peak emptying velocity more than 30 cm/sec.

Majority of patients showed no significant change in thrombus size.

None of the patients showed significant (>30%) increase in size of the thrombus during the study period.

Factors associated with failure of resolution or reduction in size include

Older age (> 40 years)

Large initial thrombus size (> 1.5 cm)

Persistent atrial fibrillation

Left atrial appendage peak emptying velocity less than 30 cm/sec

Larger left atrial dimensions and volume.

None of the patients showed evidence of thromboembolic events or any bleeding complication

during the study period.

Oral anticoagulation did not show any notable change in spontaneous echo contrast in left atrium during the study period.

IMPLICATIONS OF THE STUDY

Patients with rheumatic mitral stenosis with left atrial appendage thrombus who have valve morphology suitable for balloon mitral valvotomy or closed mitral commissurotomy can be subjected to adequate oral anticoagulation for thrombus resolution for a short period (6 to 8 weeks) if they are clinically stable. This is especially so if the patients are young, with smaller thrombus size, particularly if they are in sinus rhythm.

If the thrombus resolves, management is simplified by doing balloon mitral valvotomy or closed mitral commissurotomy, instead of open mitral valvotomy with thrombus removal in those patients.

On the other hand older patients with large left atrial appendage thrombus can be straightaway referred for open surgery especially if they are in atrial fibrillation and low left atrial appendage emptying velocity.

PROFORMA FOR PATIENT'S DATA COLLECTION

ANTICOAGULATION IN RHEUMATIC MITRAL STENOSIS WITH LEFT ATRIAL APPENDAGE THROMBUS.

Name **Age** **Sex** **Address**

Symptoms

Dyspnoea	Class	Duration
Orthopnoea		
PND		
Palpitation	Class	Duration
Odema legs		
Thromboembolic phenomena		Type
Chest pain		
Haemoptysis		
Others		

Signs

Pulse		BP	JVP	Apex
S1	A2	P2	OS	MDM
Mitral systolic murmur		TR		

ECG

TRANSTHORACIC ECHOCARDIOGRAM

Chamber dimensions & function

LV RV

RA

LA dimensions	**A4C**	**PLAX**	**PSAX**
LA area			
LA volume			

Wilkins score

Valve thickness
Calcification
Mobility
Subvalvular disease

Total

MR	**TR**	**PAP**
Other valves		

Thrombus	**Site**	**Size**	**Character**
	LA		
	LAA		
LA -SEC			

TRANSOESOPHAGEAL ECHOCARDIOGRAPHY

LA appendage **Size** **Area** **LAA Function (EF)**

LA-SEC

LAA Thrombus **Present** **Absent**

Site
Size
Character
Mobility

LA Appendage peak emptying velocity **cms /sec**

Left upper pulmonary vein flow Doppler

Any other interesting finding

Medical treatment

Digoxin Lasix Aldactone Penicilln KCL

Verapamil Others

Oral Anticoagulation;

Acitrom(Acenocomorol) mgs OD daily

Follow- up

Week

Symptom change

ACITROM Dose change

Bleeding

Thromboembolic episode

Prothrombin time and INR

Fresh ECG

Follow-up Echo (6 weeks)

Transthoracic echo

Any new finding

LA-SEC status

LAA-Thrombus Status
Size
Area
Character

Transesophageal echo

LA appendage area
Function
LA-SEC Status

LAA thrombus Present Absent

Size
Area
Character
LAA peak emptying velocity

Miscellaneous.

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